REGULATORY TOXICOLOGY AND PHARMACOLOGY 8, 447–466 (1988)

Pharmacokinetics for Regulatory Risk Analysis: The Case of Trichloroethylene

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Received November 16, 198[illegible]

Physiologically based pharmacokinetic (PBPK) models describing the uptake, metabolism, and excretion of volatile organic compounds (VOCs) are now proposed for use in regulatory health-risk assessment. A steady-state analysis of one such model is shown to provide simple, convenient predicted relationships between an applied dose and the corresponding toxicologically effective, metabolized dose for certain VOCs like trichloroethylene (TCE). A version of this PBPK model was fit to data on human metabolism of TCE to urinary metabolites in chronically exposed workers, yielding a direct estimate of PBPK parameters governing human capacity to metabolize TCE. It is shown that this estimate is consistent with others based on experimental studies of TCE metabolism in humans exposed to TCE by inhalation for short periods. These results are applied to human cancer-risk assessment using rodent bioassay data on TCE-induced tumorigenesis.

INTRODUCTION

Physiologically based pharmacokinetic (PBPK) models describing the uptake, metabolism, and excretion of volatile organic compounds (VOCs) are now proposed for use in regulatory risk assessment. Here, the PBPK approach is used to estimate the extent to which humans metabolize trichloroethylene (TCE). TCE is one of the halogenated VOCs whose metabolism, as opposed to applied dose, is directly correlated with experimentally induced chronic toxicity (Buben and O'Flaherty, 1985) and (for regulatory purposes, presumptively) carcinogenicity (U.S. EPA, 1985). For comparative purposes, similar estimates based on short-term experimental studies of TCE uptake and metabolism in humans are first summarized, and two early PBPK models applied to TCE are reviewed. A more recent PBPK model developed by Ramsey and Anderson (1984) is then described and this model's predicted behavior at steady state is analyzed. The steady-state analysis focuses on a quantity of key concern in risk analysis for VOCs like TCE, namely, the fraction of a potentially available dose that is

0273-2300/88 $3.00

actually metabolized, particularly under conditions of low-level multiroute exposure relevant to environmental regulation.

A version of the Ramsey–Andersen PBPK model is then fit to data on human metabolism of TCE to urinary metabolites in chronically exposed workers. The resulting estimate of the human capacity to metabolize TCE is shown to be consistent with earlier estimates based on the short-term, experimental studies referred to above. Finally, the steady-state analysis of the Ramsey–Andersen PBPK model is applied to an illustrative cancer-risk assessment for TCE, based on the former estimate of human metabolic capacity and on estimates of TCE's carcinogenic potency derived from rodent-bioassay data.

EXPERIMENTAL STUDIES OF TCE METABOLISM IN HUMANS

Humans metabolize TCE primarily to trichloroacetic acid (TCA) and (bound and free) trichloroethanol (TCEL), which are excreted in urine for the most part, although some TCEL and TCA may be further metabolized (Soucek and Vlachova, 1960; Bartonicek, 1962; Nomiyama and Nomiyama, 1971; Müller *et al.*, 1972; Fernandez *et al.*, 1975, 1977; Monster *et al.*, 1976, 1979). The extent to which people metabolize TCE during and after controlled respiratory exposures has been investigated by measuring total urinary metabolites generated postexposure or by quantifying the total amount of unchanged TCE expired after exposures for which total TCE retention was estimated (Soucek and Vlachova, 1960; Ogata *et al.*, 1971; Nomiyama and Nomiyama, 1971; Ertle *et al.*, 1972; Müller *et al.*, 1972; Monster *et al.*, 1976; Fernandez *et al.*, 1975, 1977; Monster *et al.*, 1979). Results from such studies are summarized in Table 1. The reported values for average percentage of retained dose metabolized (PRDM) range from 81 to 92%. Considering only the most recent studies—those by Monster *et al.* and Fernandez *et al.* involving a total of 18 males given respiratory exposures ranging from 280 to 1440 ppm-hr TCE at TCE concentrations ranging from 54 to 140 ppm—the reported values for average PRDM are remarkably consistent, ranging from 89 to 92% with a person-weighted average of 90.6 ± 1.9% (CV = 2.1%) and a corresponding individual PRDM range of 87 to 93%. These 18 individual PRDM values are not significantly correlated with either TCE exposure concentration or time-integrated TCE exposure (in ppm-hr).

PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS APPLIED TO TCE

Two early applications of the PBPK approach to TCE pharmacokinetics in humans are reviewed briefly, followed by a description of a more recent PBPK model that has been applied to TCE.

Two Early PBPK Models Applied to TCE

A PBPK model developed by Sato *et al.* (1977) was used to interpret data gathered on excretion of TCE and metabolites after respiratory exposure of four human volunteers to 100 ppm TCE for 4 hr. A first-order PBPK model was used to simulate con-

TABLE 1

TCE METABOLISM IN HUMANS AFTER EXPERIMENTAL RESPIRATORY EXPOSURE

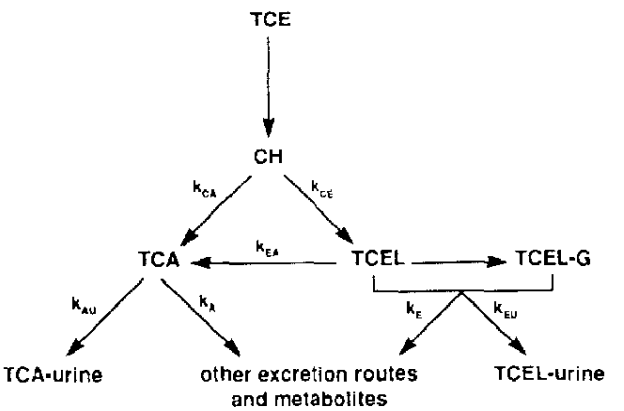
Study	TCE exposure	Collection period[a] (days)	Sex (No.)	Average % retained dose metabolized[b] = PRDM (range)
Soucek and Vlachova (1960)	93–158 ppm-5 hr	10–14	M (3)	—
			F (2)	—
Ogata *et al.* (1971)	170 ppm-3 hr	4.2	? (4)	—
	170 ppm-7 hr	4.2	? (5)	—
Nomiyama and Nomiyama (1971)	320 ppm-160 min	6	M (5)	80.8
			F (5)	87.3
Ertle *et al.* (1972)	50 ppm-6 hr for 5 days	7	M (5)	—
	100 ppm-6 hr for 5 days	7	M (5)	—
Müller *et al.* (1972)	50 ppm-6 hr for 5 days	18	M (5)	—
Monster *et al.* (1976)	70 ppm-4 hr	9	M (4)	90 (89–93)
	140 ppm-4 hr	9	M (4)	92 (91–93)
Fernandez *et al.* (1975, 1977)	54 ppm-8 hr	16	M (2)	92 (91.7–92.3)
	97 ppm-8 hr	21	M (3)	91 (90.5–93.0)
Monster *et al.* (1979)	72 ppm-4 hr for 5 days	6	M (5)	89 (88–91)

[a] Period of routine urine-collection, including exposure period. In the Monster *et al.* (1976) study, routine urine collection stopped at 66 hr, and a final sample was taken on Day 9 postexposure.

[b] Here calculated as 100% minus the reported percentage of retained TCE that is expired as TCE subsequent to exposure, for those studies reporting such a value. Retained TCE is defined in these studies as the difference between inspired and expired TCE concentration times the volume of air respired. The retained fraction, *f*, of TCE in alveolar air was reported to be about 78% (Monster *et al.*, 1976; assuming an alveolar ventilation rate of 5.9 liters/min), 71 to 78% (Fernandez *et al.*, 1975), and 70% (Monster *et al.*, 1979).

centrations in three compartments: vessel-rich (richly perfused) tissues, muscle (and other poorly perfused) tissues, and fat (very poorly perfused) tissues. In this model, the compartments are assumed to be interconnected and initially at an equilibrium determined by tissue volumes and blood/air and tissue/blood partition coefficients. The latter coefficients were based on experimental values obtained using rat and human tissues. Richly perfused tissues are assumed to be the source of both metabolic and respiratory excretion of absorbed TCE. In this model, intercompartment exchange of TCE is governed solely by postulated intertissue diffusion. When experimental human data were fitted to this model, a value of 104 liters/hr was obtained for metabolic clearance of TCE. The authors did not explain the basis for their assumption that humans exposed to TCE would have reached compartmental equilibrium after only 4 hr.

A different, more complete PBPK model was used by Fernandez *et al.* (1977) to simulate the uptake, metabolism, and excretion of TCE in experimentally exposed humans. This model contains the three compartments used by Sato *et al.* (1977), plus a liver compartment and a pulmonary compartment. The model provides for



k_{EU} = 0.0260 h^{-1}
k_{AU} = 0.00685 h^{-1}
k_E = 0.00820 h^{-1}
k_A = 0.00685 h^{-1}
k_{EA} = 0.0191 h^{-1}
$k_{CE} / (k_{CE} + k_{CA})$ = 0.78
$k_{CA} / (k_{CE} + k_{CA})$ = 0.22

FIG. 1. Pathways and rate constants for TCE metabolism used in the PBPK model of Fernandez *et al.* (1977) describing uptake, metabolism, and excretion of TCE in humans. TCE, trichloroethylene; CH, chloralhydrate; TCEL, trichloroethanol; TCEL-G, TCEL-glucuronide.

mass balance of TCE in the compartments, TCE entering and leaving the body through the lung, and TCE excreted through metabolism in the liver to metabolites excreted in urine. The uptake and excretion kinetics were assumed to be linear and governed by tissue volumes, tissue-specific blood volumes, blood perfusions, and tissue/gas partition coefficients. In the model, TCE metabolism was assumed to take place solely in the liver via the pathways shown in Fig. 1. The values for the linear kinetic parameters used by Fernandez *et al.* (1977) were determined from the available literature on TCE metabolism in humans, primarily from Müller *et al.* (1974). These values are listed in Fig. 1. In this model, TCE metabolism is assumed to be limited only by blood flow through the liver in such a way that the fraction, f_c, of arterial blood flowing into liver that is metabolically cleared of TCE is a constant equal to 0.86. The liver-perfusion value of 96.3 liters/hr used by Fernandez *et al.* (1977) for a reference 70-kg man yields a metabolic clearance rate of $96.3 f_c = 83$ liters/hr, which is close to the metabolic clearance rate of 104 liters/hr estimated by Sato *et al.* (1977). The PBPK model of Fernandez *et al.* (1977) accurately predicted the decay in alveolar-TCE concentration observed over 50 hr and the cumulative urinary excretion of TCEL and TCA observed over 200 hr after volunteers, with an average weight of about 70 kg, were exposed for 8 hr to 54 to 160 ppm TCE.

The Ramsey–Andersen PBPK Model

The National Academy of Sciences (NAS) recently considered the use of PBPK models to facilitate dose-route extrapolation when using inhalation toxicity data to

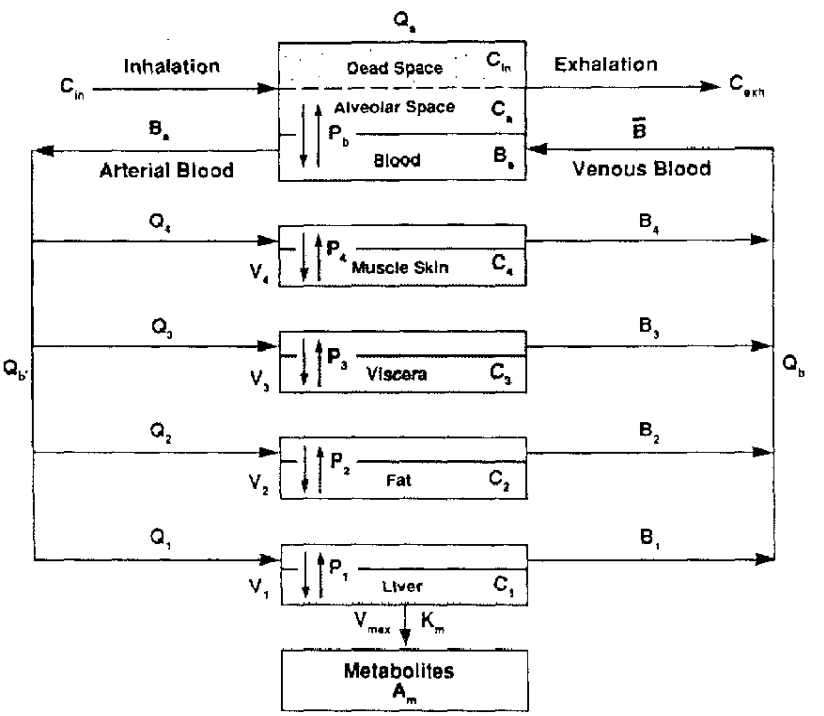


FIG. 2. Schematic diagram of physiologically based pharmacokinetic (PBPK) model for inhalation of volatile organic compounds. The model assumes that four "well-stirred" compartments or tissue groups collect inhaled compound at rates governed by air concentration (C_{in}), air and blood flows (Q), blood concentrations (B), compartment volumes (V), tissue/blood partition coefficients (P), and metabolic parameters (V_{max}, K_m).

set safe drinking water limits (NAS, 1986). A range of issues was considered in this study, including illustrative applications of the PBPK approach to dose-route extrapolation from rats to humans for noncarcinogenic toxicity associated with exposure to TCE and benzene. The pharmacokinetic model used was developed by Ramsey and Andersen (1984) to describe the uptake, metabolism, and excretion of styrene in rats and humans. The structure of the model is shown in Fig. 2, and its parameter definitions are given in Table 2. This type of model has been applied to the study and prediction of animal and human pharmacokinetics for other VOCs, including benzene, methylene chloride, and perchloroethylene (NAS, 1986; Gargas *et al.*, 1986; Andersen *et al.*, 1987; U.S. EPA, 1986a; Reitz and Nolan, 1986; Hattis *et al.*, 1986; Ward *et al.*, 1988). The model consists of a set of differential equations that describe the rate of change of the amount of absorbed chemical present in each of four physiologically realistic tissue compartments, which are assumed to be ideally well-mixed at any given time. Metabolism is presumed to occur solely in the liver through a saturable enzymatic process with Michaelis–Menten kinetics.

According to the Ramsey–Andersen model, pulmonary uptake of a VOC occurs continuously such that alveolar concentration, C_a, is in instantaneous equilibrium with arterial blood concentration, B_a, governed by the blood/air partition coefficient,

TABLE 2

COMPARTMENT AND PARAMETER DEFINITIONS FOR THE RAMSEY–ANDERSEN PBPK MODEL

Abbrev.	Definition	Unit
C_{in}	Concentration in air inhaled	mg/liter air
C_a	Concentration in alveolar air	mg/liter air
C_{exh}	Measured concentration in expired breath	mg/liter air
Q_a	Alveolar ventilation rate	liters air/hr
Q_b	Cardiac output	liters blood/hr
P_b	Blood/air partition coefficient	liters air/liter blood
B_a	Arterial blood concentration	mg/liter blood
$\bar{B}$	Venous blood concentration	mg/liter blood
A_m	Amount metabolized in liver	mg
Q	Blood flow rate to compartment i	liters blood/hr
V	Volume of compartment i	liters (= kg)
C	Concentration in compartment i	mg/liter
B	Concentration in venous blood leaving compartment i	mg/liter blood
A	Amount in compartment i	mg
P	Tissue/blood partition coefficient for compartment i	liters blood/liter tissue i
V_{max}	Maximum metabolic rate	mg/hr
K_m	Michaelis constant (B_l (dA_m/dt = V_{max} 2))	mg/liter blood

Compartmental subscripts
i 1 Liver (metabolizing tissue group)
2 Fat tissue (very poorly perfused)
3 Richly perfused tissues (brain, kidney, viscera)
4 Poorly perfused tissues (muscle, skin)

P_b, in accordance with the relation $C_a = B_a/P_b$. Similarly, the concentrations, C_i, of chemical in each tissue compartment are presumed to be in instantaneous equilibrium with the concentrations, B_i, in venous blood exiting the corresponding tissue, governed by the corresponding tissue/blood partition coefficients such that $B_i = C_i/P_i$. The amount of chemical in any given tissue compartment is given by $A_i = C_iV_i$. For notational convenience, the dependence of state variables (C's, B's, and A's) on time t is suppressed.

In any given interval, dt, a VOC delivered to the lung via respiratory retention and via returning venous blood is balanced in this model by the chemical mass exiting the lung via exhalation and via arterial blood, such that $(Q_aC_{in} + Q_b\bar{B})dt = (Q_aC_a + Q_bB_a)dt$, or $Q_a(C_{in} - C_a) = Q_b(B_a - \bar{B})$, which, recalling that $C_a = B_a/P_b$, yields

$$B_a = \frac{Q_aC_{in} + Q_b\bar{B}}{(Q_a/P_b) + Q_b}. \quad (1)$$

(Note that an experimentally measured concentration in exhaled breath is given by $C_{exh} = F_dC_{in} + (1 - F_d)C_a$, where the dilution factor F_d approaches zero as the efficiency of measuring purely alveolar expired air approaches 100%.) Equation (1) specifies B_a (and thus C_a and C_{exh}) to be at each instant a flow-weighted average of C_{in} and $\bar{B}$. Similarly, the concentration $\bar{B}$ in venous blood returning from each compartment is presumed to be the instantaneous flow-weighted average

$$\bar{B} = \frac{1}{Q_b} \sum_{i=1}^{4} Q_i B_i. \tag{2}$$

For the nonmetabolizing tissues, the amount of chemical entering the ith compartment via arterial blood during any given interval is set equal to the amount gained by that compartment plus the amount leaving in venous blood. The chemical concentration in venous blood leaving each of these compartments is therefore defined by

$$\dot{B}_i = \frac{Q_i}{V_i P_i} (B_a - B_i), \qquad i = 2, 3, 4, \tag{3}$$

where dot notation is used here, and below, to represent differentiation with respect to time (i.e., $\dot{B}_i = dB_i/dt$, etc.). The amount of chemical metabolized in liver is given by the Michaelis–Menten relation

$$\dot{A}_m = \frac{V_{max} B_1}{K_m + B_1}. \tag{4}$$

in which K_m is defined as the concentration in venous blood from liver (or, alternatively, $K_m P_1$ is the chemical concentration in liver) at which the liver's metabolic velocity $\dot{A}_m$ is one-half its maximum value, V_{max}. The state equation for venous liver blood concentration is thus given by

$$\dot{B}_1 = \frac{Q_1}{V_1 P_1} (B_a - B_1) - \frac{\dot{A}_m}{V_1 P_1}. \tag{5}$$

The system of Eqs. (1)–(5) represents the PBPK model for inhalation of a VOC, and for any given time its compartmental quantities A_i, or corresponding concentrations B_i or C_i, are found by simultaneous numerical integration of the system.

Exposure by routes other than inhalation is easily incorporated into this model. Since blood draining the stomach, small intestine, and colon passes through the hepatic portal vein, exposure to VOCs via ingestion is modeled simply by assuming a direct introduction of the ingested mass into the liver compartment (NAS, 1986). The latter introduction can be assumed to reflect a first-order infusion process, the approach taken in NAS (1986), or it may be modeled more simply as a constant infusion into the liver at a rate R (mg/hr) by adding the constant $R/(V_1 P_1)$ to the right side of Eq. (5).

Pharmacokinetic Quantities of Regulatory Concern

Of particular interest, in the context of regulatory risk assessment for certain suspected environmental carcinogens like TCE, is the metabolized fraction of the total quantity of chemical potentially available for absorption and metabolism. Under conditions of purely respiratory exposure the corresponding quantity of interest is the fraction, f_{mr}, of the maximum plausible metabolic rate, or metabolic clearance fraction, given a constant ambient concentration C_{in}. For the Ramsey–Andersen PBPK model, this quantity may be defined as

$$f_{mr} = \dot{A}_m/(Q_a C_{in}), \tag{6}$$

which may be contrasted with the assumption, sometimes made in the context of carcinogen-risk assessment (Anderson *et al.*, 1983), that 100% of a chemical entering the lungs through total respiratory ventilation (or that contained in approximately 20 m^3/day for a reference 70-kg man) is absorbed and potentially available for metabolism.

In the context of purely ingestive exposure, a corresponding (hypothetical) quantity may be defined as the fraction, f_{mo}, of the maximum plausible metabolic rate given a continuous rate, R, of ingestive absorption. Again by the Ramsey–Andersen model, this quantity would be defined as

$$f_{mo} = \dot{A}_m/R. \tag{7}$$

Because ingestion is actually a discontinuous process with some average absorption rate R, the maximum plausible metabolic rate will be less than f_{mo} as defined by Eq. (7) to the extent that metabolic saturation occurs, allowing more of the dose to escape via exhalation and thus to avoid being metabolized. For VOCs, both f_{mr} and f_{mo} are necessarily less than one whenever (finite) metabolism takes place, because any unmetabolized compound is always subject to pulmonary excretion.

ANALYSIS OF THE RAMSEY–ANDERSEN PBPK MODEL AT STEADY STATE

Very low-level, continuous exposure scenarios are typically of concern in the context of environmental regulation. The following is an analysis of how the Ramsey–Andersen PBPK model behaves under steady-state, respiratory exposure conditions. Steady-state ingestive exposure, using the constant infusion model described earlier, is also considered for the purpose of comparison and because the mixed exposure case represents a scenario of human environmental exposure which may be of particular regulatory concern.

Because at steady state $B_a = B_i$ for $i = 2, 3, 4$, Eq. (2) reduces under steady-state conditions to

$$\bar{B} = \frac{1}{Q_b}[Q_l B_l + B_a(Q_b - Q_l)], \tag{8}$$

so that Eq. (1) reduces to

$$B_a = \frac{Q_a C_{in} + Q_l B_l}{(Q_a/P_b) + Q_l}. \tag{9}$$

Also at steady state, Eq. (5), modified as described above to reflect constant ingestive infusion, reduces to the form

$$\frac{V_{max} B_l}{K_m + B_l} = Q_l(B_a - B_l) + R, \tag{10}$$

so that the solution for venous liver blood concentration, given input C_{in}, is the quadratic root

$$B_1 = Y + \sqrt{Y^2 + Z}, \tag{11a}$$

in which

$$Y = \frac{1}{2}[C_{in}P_b + (R - V_{max})W - K_m], \tag{11b}$$

$$Z = K_m(C_{in}P_b + RW), \tag{11c}$$

and

$$W = \left(\frac{P_b}{Q_a} + \frac{1}{Q_1}\right). \tag{11d}$$

Note that the parameters Q_b, V_i, and P_i for $i = 1, \ldots, 4$ and Q_i for $i = 1, 2, 3$ do not appear in this solution. The steady-state metabolic rate is thus given by using Eqs. (11a)–(11d) to evaluate B_1 in Eq. (4), and likewise in the expressions for the fractions f_{mr} and f_{mo} of maximal metabolic rate for TCE given by Eqs. (6) and (7), respectively.

Important in the context of environmental risk management is the limiting value of f_{mr} as $C_{in} \to 0$, that is, at very low exposure levels that might be typical of nonoccupational, purely respiratory exposure to VOCs. At such exposure levels, metabolism is essentially a linear function of applied dose in the Ramsey–Andersen PBPK model. In this discussion of the low-dose situation, the ratio (V_{max}/K_m) shall be represented by the linear metabolic clearance rate K (in liters/hr). The limiting value referred to is given by

$$f^*_{mr} = \lim_{C_{in} \to 0} f_{mr} = \left[1 + \frac{Q_a}{P_b}\left(\frac{1}{K} + \frac{1}{Q_1}\right)\right]^{-1}, \tag{12}$$

whereas the maximally conservative assumption that infinite metabolism is approached as steady-state $C_{in} \to 0$ yields the corresponding limiting value

$$f^{**}_{mr} = \lim_{K \to \infty} f^*_{mr} = \left[1 + \frac{(Q_a/Q_1)}{P_b}\right]^{-1}, \tag{13}$$

representing the physiologically determined upper bound on the fraction of respiratory intake capable of being metabolized. This value is a function of just three parameters, only one of which is influenced by the particular chemical under consideration. Note that f^*_{mr} and f^{**}_{mr} also apply to a VOC dose received via dermal absorption, since such a dose would enter systemic circulation and thus be subject to pulmonary excretion in the same way that a respired dose would.

The consequences of the Ramsey–Andersen model for purely respiratory exposure suggested by Eqs. (12) and (13) are in contrast to the assumption regarding TCE metabolism made in the Fernandez *et al.* (1977) model, discussed earlier. Recall that the latter model presumed a purely flow-limited metabolic clearance fraction of $f_c = 0.86$ (with a corresponding metabolic rate of $f_c Q_1 B_a$, in the notation used to describe the Ramsey–Andersen model). This assumption is different from the implication of Eqs. (12) and (13) that metabolic clearance of a respired VOC is directly (but nonlinearly) proportional to the corresponding clearance rate parameter, K, and only becomes constant as $K \to \infty$. Indeed, under steady-state conditions of respiratory exposure, Eq. (5) implies that the relation

$$f_c = \frac{Q_l(B_a - B_l)}{Q_l B_a} = \frac{K}{K + Q_l} \tag{14}$$

follows from the Ramsey–Andersen PBPK model. Note that, using Eq. (14), Eq. (12) may be rewritten as

$$f^*_{mr} = \left[1 + \frac{(Q_a/Q_l)}{P_b f_c}\right]^{-1}. \tag{15}$$

which, compared with Eq. (13), clearly shows that f^*_{mr} approaches its maximal value, f^{**}_{mr}, only as f_c approaches unity.

The expression for f^*_{mr} given in Eq. (12) may be compared to a similar limiting value of f_{mo} as a hypothetically continuous, purely ingestive dose approaches zero. It can be shown that this limiting value is given by

$$f^*_{mo} = \lim_{R \to 0} f_{mo} = \left[1 + \frac{1}{K}\left(\frac{P_b}{Q_a} + \frac{1}{Q_l}\right)^{-1}\right]^{-1}. \tag{16}$$

Therefore, $f^*_{mo} > f^*_{mr}$, and f^*_{mo} approaches unity under the maximally conservative assumption that $K \to \infty$ as $R \to 0$. That is, unlike the case of purely respiratory exposure, it is physiologically plausible that close to 100% of a low-level, continuously ingested dose of a VOC can be metabolized. This is true because of a "first-pass" effect on ingested VOC doses, whereby they are collected in blood draining the gastrointestinal tract and transported through the hepatic portal vein directly to the liver, before being passed to mixed venous blood where they become subject to respiratory elimination.

In the case of mixed respiratory and ingestive exposure under steady-state conditions, the fraction, f_m, of the maximum plausible metabolic rate is the weighted average

$$f_m = \frac{f_{mr} Q_a C_{in} + f_{mo} R}{Q_a C_{in} + R},$$

which, as $C_{in} \to 0$ and $R \to 0$, approaches the limiting value

$$f^*_m = \frac{f^*_{mr} Q_a C_{in} + f^*_{mo} R}{Q_a C_{in} + R}, \tag{17}$$

where $f_m < f^*_m$. Equation (17) remains approximately true when C_{in} and R are replaced by their corresponding time-weighted average values,

$$\bar{C}_{in} = \int_0^T C_{in}(t)\,dt \quad \text{and} \quad \bar{R} = \int_0^T R(t)\,dt,$$

provided that temporal discontinuity in $C_{in}(t)$ and $R(t)$ does not result in a significant deviation from linear, nonsaturated metabolism (i.e., provided that $\{B_l(t) \mid (C_{in}(t), R(t), t)\} \ll K_m$ for all t where $0 \leq t \leq T$). To the extent that metabolic saturation does take place, the latter approximation will be less than the value f^*_m defined by Eq. (17).

Note that the quantities f^*_{mr}, f^{**}_{mr}, f^*_{mo}, f^{**}_{mo}, f^*_m, and f_c defined above are all invariant with respect to body weight, so long as rates for flows and metabolic processes (e.g., Q_a, Q_b, Q_l, V_{max}, K) are all assumed to scale to the same 0.7 power of

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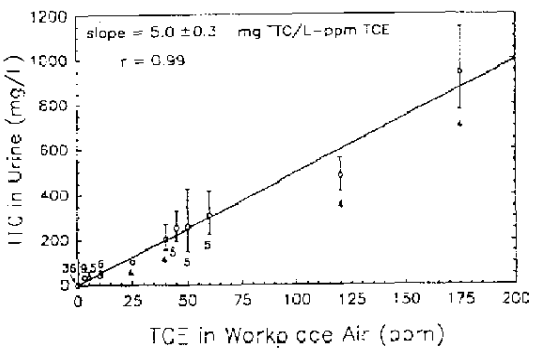

FIG. 3. Data of Ikeda *et al.* (1972) on geometric mean levels of total trichloro compounds (TTC) in urine produced in 51 male Japanese workers exposed 8 hr/day, 6 days/week to different daily time-weighted average concentrations of trichloroethylene (TCE) in air. Numbers next to data points indicate the number of workers monitored at the corresponding concentration level. Error bars represent ±one geometric standard deviation. Linear, least-squares regression line shown for unweighted data points.

body weight.[1] By the same reasoning, the quantities f_{mr}, f_{m10}, and f_m are also invariant with respect to body weight whenever the pharmacokinetic system involved is entirely linear, or nonsaturated. It also follows that f^*_{m10} remains invariant with body weight when both A_m and R are in units of milligrams per kilogram per day, whereas A_m in milligrams per kilogram per day will be smaller for the larger of two animals exposed to a given very low concentration, C_{in}, of VOC in air by the factor $(w_1/w_2)^{0.3}$, where w_1 and w_2 are the weights of the smaller and larger animals, respectively.

APPLICATION OF PBPK MODEL TO HUMAN DATA ON TCE METABOLISM

Data are available on the extent to which urinary metabolites are produced in workers exposed to TCE in air at concentrations of 0 to 175 ppm (Ikeda *et al.*, 1972; Ikeda, 1977). These data, shown in Fig. 3, are derived from surveys of workplace air

[1] This approach is often taken because, in the context of pharmacokinetic modeling, such physiological parameters are generally assumed to vary with basal metabolic rate in proportion to body surface area (or, approximately, to body weight to the 0.7 power), rather than to body weight per se (Gehring et al., 1978; Dedrick and Bischoff, 1980; Andersen *et al.*, 1980; Andersen, 1981; Calabrese, 1983; Ramsey and Andersen, 1984; U.S. EPA, 1985, 1986a; NAS, 1986). For example, given an estimated V_{max} in milligrams per hour for an animal of weight w_1, the corresponding predicted values for animals of weight w_2 would be $V_{max}(w_2/w_1)^{0.7}$ (in mg/hr) or, on a weight-normalized basis, $(V_{max}/w_1)(w_2/w_2)^{0.3}$ (in mg/kg-hr). That is, a heavier animal would be expected to metabolize less per unit body weight than a lighter one in a given amount of time. In contrast, the value of the Michaelis constant, K_m, for a given compound, in the absence of data indicating otherwise, is generally assumed to be independent of body size when this constant is expressed as the reactant concentration (in mg/liter blood) at which the metabolic reaction rate is one-half its maximal value (Ramsey and Andersen, 1984; U.S. EPA, 1986a; NAS, 1986). Since blood weight varies with body weight approximately to the first power for animals of widely varying weights (Dedrick and Bischoff, 1980), the independence of K_m and body size should also be expected to hold for K_m values expressed in terms of milligrams per kilogram body weight. If the physiological clearance parameters are

and urine samples collected from 51 male workers in 10 TCE workshops in Japan. Workplace air concentrations of TCE were reported to be relatively constant over the common 8 hr/day, 6 days/week occupational schedule of the workers studied. Urine samples were passed at about 1:00 p.m. in the "latter half of a week" (Ikeda *et al.*, 1972). Concentrations of metabolites (TCEL, TCA, and TTC) in urine were measured and plotted against time-weighted average TCE–air concentrations. The relationship between the reported geometric mean TTC levels in urine (adjusted to a specific gravity of 1.016) and corresponding ambient TCE concentrations ranging from 0 to 175 ppm is well represented by a 0-intercept-regression line with a slope of 5.0 mg TTC/liter urine/ppm TCE in air (Fig. 3).

A PBPK model based on the Ramsey–Andersen model was adapted, as described below, to model TCE pharmacokinetics in humans occupationally exposed to ambient TCE at the levels and in the temporal pattern experienced by the Japanese workers observed by Ikeda *et al.* (1972). For this analysis, the Ramsey–Andersen model was extended to include the TCE-metabolism model used by Fernandez *et al.* (1977), discussed above and illustrated in Fig. 1. An explicit model of human urinary output was also included as well as a urine-sampling scheme similar to that used in the Ikeda *et al.* study.

Reference values for the parameters listed in Table 2 and used in the PBPK model for TCE-exposed workers are given in Table 3. The values for the physiological parameters Q_a, Q_b, Q_t, and V_t pertaining to a reference 70-kg male worker appearing in Table 3 are taken from a study by Ward *et al.* (1988), who examined a PBPK model for humans exposed to perchloroethylene; these values are similar to those used in the NAS (1986) analysis. The values for the blood/air and fat/blood partition coefficients (P_b and P_2) for TCE were taken from U.S. EPA (1985), as adapted from Sato *et al.* (1977). The values used for P_1 and P_4 are based on the liver/blood, muscle/blood, and blood/air partition coefficients for rats (equal to 1.69, 0.63, and 25.82, respectively) reported by Sato *et al.* (1977), under the assumption that the corresponding tissue/air partition coefficients for rats and humans are equal. (Supporting this assumption is the fact that the fat/air partition coefficients for rats and humans are 661 and 674, respectively, as reported by Sato *et al.*). Similarly, the value used for P_3 is based on an average tissue/blood partition coefficient of 1.26 for rat visceral tissues calculated from the data of Sato *et al.* Finally, the metabolic rate-parameter values used by Fernandez *et al.* (1977), and shown in Fig. 1, were used to represent those of a reference 70-kg worker.

It was assumed that a 70-kg male produces an average of 0.0583 liter urine per hour during the day, for urine adjusted to a specific gravity of 1.016 (ICRP, 1975). In the absence of more specific data, it was further assumed that urine samples were passed by the workers studied by Ikeda *et al.* (1972) at 1:00 p.m. on Thursdays, Fridays, and Saturdays of each week, and that a prior urination (emptying the bladder) occurred 4 hr before (i.e., at 9:00 a.m.) on each collection day for all workers.

For the purpose of modeling the occupational exposures studies by Ikeda *et al.* (1972), the reference parameter values listed in Table 3 were scaled to approximate

assumed to be directly proportional to the 0.7 power of body weight, it follows that kinetic rate constants governing uptake, metabolism, and excretion—all in units of per hour, or liters per hour per liter compartment volume where 1 liter body volume is assumed to weigh about 1 kg—are inversely proportional to the 0.3 power of body weight.

TABLE 3

PARAMETER VALUES USED IN PBPK MODEL FOR TCE

Parameter	Unit	Reference rat[a]	Male reference human[b]	Japanese male worker[c]
W (weight body)	kg	0.30	70	55.2
Q_a	liters/hr	5.74	353.5	299.3
Q_b	liters/hr	5.74	371.6	314.7
P_b		22.0	9.92	9.92
Q_i/Q_b, i = 1		0.25	0.25	0.25
2		0.09	0.05	0.04
3		0.47	0.51	0.52
4		0.19	0.19	0.19
V_i/W, i = 1		0.041	0.04	0.027
2		0.09	0.20	0.15
3		0.059	0.05	0.10
4		0.72	0.62	0.61
P_i, i = 1		1.3	4.40	4.40
2		26	68.0	68.0
3		1.3	3.28	3.28
4		0.5	1.64	1.64
V_{max}	mg/hr	5.17	—	—
K_m	mg/liter	0.25	—	—

[a] Parameter values taken from NAS (1986); metabolic parameters were reported to be determined by gas uptake experiments (NAS, 1986).

[b] Physiological parameter values taken from Ward *et al.* (1988); values for partition coefficients are based on those listed in U.S. EPA (1985), derived from Sato *et al.* (1977).

[c] Parameter values are scaled from those corresponding to a reference male human, based on the anatomical model of Kerr (1979) for reference Japanese adults.

those applicable to a typical Japanese male worker. To this end, body weight was set at 55.2 kg and the tissue volumes V_i were adjusted to the new values shown in Table 3, based on an anatomical model for reference Japanese adults developed by Kerr (1979). As shown in Table 3, the values for the blood-flow fractions Q_2/Q_b and Q_3/Q_b were changed slightly to reflect the altered tissue volumes. The reference flow rates Q_a and Q_b and that for urinary output were all decreased by the factor $(55.2/70)^{0.7}$, and the reference rate constants for metabolism (appearing in Fig. 1) were all increased by the factor $(70/55.2)^{0.3}$, for the reasons discussed at the end of the previous section.

Workers were assumed to be exposed to TCE from 8:00 a.m. to 12:00 noon and 1:00 to 5:00 p.m. (i.e., 8 hr/day with a 1-hr lunch break) on Monday through Saturday of each week. To approximate conditions of dynamic equilibrium, the occupational exposure scenario was run for a simulated 5-week period. Numerical integration of the system of differential equations involved was done on a VAX 11/750 computer using a variable-step Gear method (Hindmarsh, 1983). On each of the last 3 urine collection days of the simulation, calculated urinary concentrations of TCA and TCEL (adjusting for the molecular weight difference between these metabolites and TCE) were added and the three sums were averaged to yield a predicted concentration of TTC in urine corresponding to any given input value for the metabolic clearance parameter $K = (V_{max}/K_m)$.

The PBPK model described was used to estimate a unique value of K that allowed the model to predict a metabolic output of 5.0 mg TTC/liter urine/ppm TCE, consistent with the data of Ikeda *et al.* (1972) for workers exposed to TCE in the manner described above. The estimate of K we obtained is 47,000 liters/hr, which, from Eq. (14), implies that 99.8%, i.e., virtually all, the TCE in blood entering the liver is metabolized in humans so exposed.

APPLICATION OF PBPK APPROACH TO CANCER-RISK ASSESSMENT FOR TCE

Metabolized Dose in Humans

On the basis of the foregoing analysis of TCE metabolism in humans, a good estimate of the metabolized fraction f^*_{mr} of TCE inhaled by humans at ambient concentration levels of 0 to 175 ppm (and of dermally absorbed TCE at similarly low exposure levels) is provided by Eq. (13) to be about 72%. This value of 72% is somewhat less than the mean value of 91% (range 87 to 93%) for the "percentage of retained dose metabolized" (PRDM) based on the data from three studies of TCE metabolism in experimentally exposed humans discussed earlier and summarized in Table 1. This discrepancy is explained by the fact that, by definition, $f_{mr} \neq$ PRDM, because PRDM already takes into account that only a (time-dependent) fraction, f_r, of respired air is cleared of TCE to constitute the "retained" TCE dose referred to by PRDM, such that f_{mr} = PRDM $\times f_r$. If it is assumed that the average value of f_r was approximately 0.78 for the three studies referred to (see Table 1, footnote *b*), then the product PRDM $\times f_r$ equals about 71%, which is consistent with the estimate of 72% derived above.

Again using the estimate of K obtained above to describe the Ikeda *et al.* data, the fraction f^*_{mo} of ingested TCE that is metabolized by humans is given by Eq. (16) to be approximately 100%. Consequently, for humans subject to low levels of TCE exposure by both respiratory and ingestion pathways, Eq. (17) may be rewritten as

$$24\dot{A}_m = 24(0.72Q_a\bar{C}_{in} + \bar{R}) \tag{18a}$$

or

$$24\dot{A}_m = 17Q_a\bar{C}_{in} + 2C_w, \tag{18b}$$

which represent the daily dose of TCE metabolized (in mg/day), given a daily, time-weighted average ambient concentration $\bar{C}_{in}$ (in mg/liter) and ingestion rate $\bar{R}$ (in mg/hr) or water concentration C_w (in mg/liter = $12\bar{R}$, assuming ingestion of 2 liters/day).

Carcinogenic Potency Estimation

To assess potential increased lifetime cancer risk (ILCR) to humans from known rodent carcinogens in the absence of adequate epidemiological data, risk may be extrapolated on the basis of tumor response data from rodent bioassays (Andersen *et*

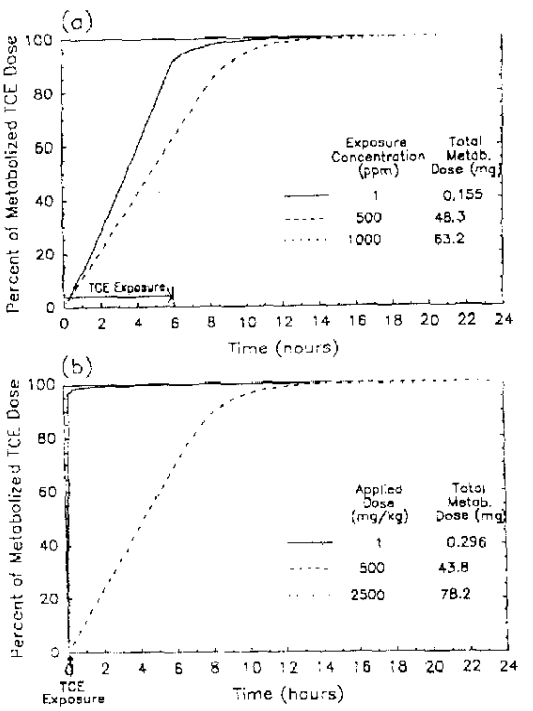

FIG. 4. Simulation of metabolism of trichloroethylene (TCE) in a 0.30-kg rat exposed via (a) inhalation and (b) ingestion, using the Ramsey–Andersen PBPK model with the parameter values listed in Table 3.

al., 1983; U.S. EPA, 1986b), of which several have been carried out in the case of TCE (NCI, 1976; Bell *et al.*, 1978; Henschler *et al.*, 1980; NTP, 1983; Fukuda, 1983; Maltoni *et al.*, 1986). However, for metabolically activated compounds like TCE, each applied, lifetime time-weighted average (LTWA) dose rate used in the bioassays must first be converted to a corresponding effective dose rate, M, of TCE metabolites, either in milligrams per kilogram per day or milligrams per square meter per day (using, respectively, a body-weight or surface-area approach to interspecies extrapolation of doses assumed to be equipotent with respect to eliciting a tumorigenic response). Data from mass-balance studies of TCE metabolism in rodents dosed with radiolabeled TCE may be used to convert D to M, provided that the test species and strains are the same and that either (i) the exposure regimens and the animal weights used in the metabolite studies and the bioassay are identical or (ii) the pharmacokinetics involved are sufficiently invariant with respect to exposure duration and body weight that f_{mr} and f_{mo} are not expected to vary from one exposure scenario to another for animals of differing weight.

Simulations using the Ramsey–Andersen PBPK model, with the parameter values for a reference rat listed in Table 3, predict that rats (and hence mice, which weigh less than rats) dosed with TCE by gavage or inhalation at the levels and in the temporal patterns used in the TCE cancer bioassays cited metabolize 100% of retained TCE

TABLE 4

BIOASSAY DOSE–RESPONSE DATA AND CORRESPONDING ESTIMATES OF CARCINOGENIC POTENCY FOR TCE

Study, species, strain	Sex, weight (dosed animals)	Daily experimental applied dose or Concn., D	LTWA metabolized dose[a], M (mg/kg-day)	Tumor		95% UCL potency[d] of metabolized dose $q_1^*(M)$ (mg M/kg-day)$^{-1}$	
				Type[b]	Incidence[c]	BW[e]	SA[f]
NCI 1976, mice, B6C3F1	M, 34 g	0 mg/kg	0		1/20		
		1169 mg/kg	369.6	HCC	26/48	0.0025	0.032
		2339 mg/kg	739.4		31/40		
					TT-IT	0.0033	0.042
					TT-LT	0.00034	0.0044
	F, 29 g	0 mg/kg	0		0/18		
		869 mg/kg	274.7	HCC	4/42	0.00073	0.0098
		1739 mg/kg	549.8		11/37		
NTP 1983, mice, B6C3F1	M, 37 g	0 mg/kg	0		8/48		
		1000 mg/kg	563	HCC	30/50	0.0019	0.023
					TT-IT	0.0029	0.036
					TT-LT	0.0013	0.016
		0 mg/kg	0	HCC or	11/48		
		1000 mg/kg	563	HCA	38/50	0.0029	0.036
					TT-IT	0.0048	0.059
					TT-LT	0.0018	0.022
	F, 33 g	0 mg/kg	0		2/41		
		1000 mg/kg	563	HCC	13/41	0.00096	0.012
					TT-IT	0.0011	0.014
					TT-LT	0.00077	0.0099
		0 mg/kg	0	HCC or	4/41		
		1000 mg/kg	563	HCA	19/41	0.0014	0.018
					TT-IT	0.0019	0.024
					TT-LT	0.0011	0.014
NTP 1983, rats, F344/N	M, 340 g	0 mg/kg	0		0/33		
		500 mg/kg	198	RTC	0/20	0.00074	0.0043
		1000 mg/kg	282		3/16		
		0 mg/kg	0		0/45		
		500 mg/kg	198	RTC or	2/39	0.00065	0.0038
		1000 mg/kg	282	RTA	3/26		
					TT-IT	0.00034	0.0020
					TT-LT	0.00068	0.0040
Bell *et al.* 1978, mice, B6C3F1	M, 35 g (?)	0 ppmv-6 hr	0		18/99		
		100 ppmv-6 hr	42.3		28/95		
		300 ppmv-6 hr	127	HCC	31/100	0.0020	0.026
		600 ppmv-6 hr	254		43/97		
		0 ppmv-6 hr	0		20/99		
		100 ppmv-6 hr	42.3	HCC or	35/95		
		300 ppmv-6 hr	127	HCA	38/100	0.0028	0.036
		600 ppmv-6 hr	254		53/97		
Henschler *et al* 1980, mice, Han:NMRI	F, 30 g (?)	0 ppmv-6 hr	0		9/29		
		100 ppmv-6 hr	33.2	ML	17/30	0.0074	0.098
		500 ppmv-6 hr	166		18/28		
Fukuda *et al.* 1983, mice, ICR	F, 30 g (?)	0 ppmv-7 hr	0		1/49		
		50 ppmv-7 hr	25.8		3/50		
		150 ppmv-7 hr	77.4	LA	8/50	0.0014	0.019
		450 ppmv-7 hr	232		7/46		

TABLE 4—*Continued*

Study, species, strain	Sex, weight (dosed animals)	Daily experimental applied dose or Concn., D	LTWA metabolized dose[a], M (mg/kg-day)	Tumor		95% UCL potency[d] of metabolized dose $q_1^*(M)$ (mg M/kg-day)$^{-1}$	
				Type[b]	Incidence[c]	BW[e]	SA[f]
Maltoni *et al.* 1986, mice, Swiss	M, 41 g	0 ppmv-7 hr	0		4/90		
		100 ppmv-7 hr	35.3		2/90		
		300 ppmv-7 hr	106	MH	8/90	0.00082	0.0098
		600 ppmv-7 hr	212		13/90		

[a] Lifetime, time-weighted-average metabolized dose, M, in mg/kg-day. See Bogen *et al.* (1988) for details on derivation as a function of D.

[b] HCC, hepatocellular carcinoma; HCA, hepatocellular adenoma; RTC, renal tubular-cell adenocarcinoma; RTA, renal tubular-cell adenoma; ML, malignant lymphoma; LA, lung adenocarcinoma; MH, malignant hepatoma.

[c] Tumor-incidence denominator excludes animals dying before the occurrence of the first corresponding tumor type observed in the NCI (1976) and NTP (1983) studies. TT–IT, time-to-tumor data using an "incidental-tumor" model; TT–LT, time-to-tumor data using a "lethal-tumor" model.

[d] "Potency" here means the low-dose dose–response slope expressed by an upper-bound linear multistage coefficient such that at very low doses, risk = (potency) × dose), according to a multistage (or, with time-to-tumor data as input, a time-dependent multistage) risk-prediction model (Crump and Watson, 1979; U.S. EPA, 1980; Anderson *et al.*, 1983; Howe and Crump, 1983; Crump and Howe, 1984). 95% UCL, one-tailed 95% upper confidence limit.

[e] BW, body weight interspecies dose-extrapolation method; equivalent doses assumed to be in mg/kg, so $M_{human} = M_{animal}$.

[f] SA, surface area interspecies dose-extrapolation method; equivalent doses assumed to be in mg/kg$^{2/3}$, so $M_{human} = M_{animal}$[(animal weight)/70 kg]$^{1/3}$.

within 24 hr (Fig. 4). Thus, no buildup of residual TCE within body tissues upon repeated daily dosing is expected. This prediction is supported by experimental data on TCE metabolism in B6C3F1 mice given daily gavage doses of TCE for 1, 10, and 180 days (Green and Prout, 1985). Recalling that f^*_{mo} and f^*_{mr} are invariant with respect to body weight, it follows, under conditions of linear metabolic kinetics, that data on TCE metabolism from single-exposure mass-balance studies may be extrapolated directly to the rodent-bioassay context (correcting for nonexposure days). The data of Prout *et al.* (1985) clearly demonstrate that TCE metabolism in mice is unsaturated even at very high levels of TCE exposure. Furthermore, PBPK simulations revealed that small changes in rodent body weight do not influence predicted values of f_{mo} and f_{mr}, even at high levels of TCE exposure involving metabolic saturation in rats. Thus, experimental metabolism data may be used to predict the extent of TCE metabolism in rats and mice under the exposure conditions of the TCE bioassays cited.

Prediction of Human Cancer Risk

Based on the rodent-bioassay data for TCE carcinogenicity cited above and on mass-balance studies of TCE metabolism in B6C3F1 mice and Osborne–Mendel rats exposed via single gavage or inhalation administrations of TCE (Prout *et al.*, 1985;

Stott *et al.*, 1982), upper-bound carcinogenic potencies for TCE in rodents were calculated (Bogen *et al.*, 1988) and are listed in Table 4. Each of the 50 alternative potency values shown is a function of M and tumor-incidence data for rodents in a given bioassay. The values range from 0.00034 to 0.098 $(\text{mg/kg-day})^{-1}$ (a 290-fold range). These values may be used directly with estimated values of M for humans in order to derive estimates of (upper-bound) ILCR associated with exposure to TCE. For example, if a LTWA exposure to 1 $\mu g/m^3$ (5.38 ppb) TCE in air and 1 μg/liter TCE in water is assumed, along with LTWA alveolar ventilation and water consumption rates of 5.05 liters/kg-hr (from Table 3) and 2 liters/70 kg-day, respectively, then Eq. (18b) and the potencies from Table 4 yield a corresponding predicted ILCR between 3.9×10^{-8} and 1.1×10^{-5}.

DISCUSSION

Application of a PBPK approach to the estimation of VOC metabolism in humans may provide simple, convenient relationships between applied and toxicologically effective VOC doses under low-level exposure conditions pertinent to environmental regulation. Parameterizations of PBPK model of TCE metabolism in humans, using human data on TCE metabolism after chronic exposure to between 0 and 175 ppm TCE in workplace air, predict that approximately 100% of TCE entering the liver, or about 72% of alveolarly respired TCE, is metabolized. This prediction in accordance with experimental data on TCE metabolism obtained using humans exposed to TCE for short periods. The linear metabolic kinetics observed for TCE metabolism at occupational exposures of up to 175 ppm TCE differ from those predicted for tetrachloroethylene using a similar PBPK approach: the latter kinetics have been shown to involve saturation at occupational exposure levels between 10 and 100 ppm in air (Bogen and McKone, 1987). Nevertheless, linear pharmacokinetics are expected for both compounds, and probably for many other halogenated VOCs as well, at the very low exposure levels of environmental regulatory concern. This fact often allows a simplified PBPK approach, of the type outlined here, to be adopted in addressing problems of regulatory toxicology such as environmental carcinogen-risk assessment for VOCs.

ACKNOWLEDGMENTS

This work was performed under the auspices of the U.S. Department of Energy by the Lawrence Livermore National Laboratory under Contract W-7405-Eng-48. Funding was provided by the U.S. Air Force, Harry G. Armstrong Aerospace Medical Research Laboratory, Toxic Hazards Division.

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